CLAIMS

We claim:

1. An isolated nucleic acid molecule selected from the group consisting of:

(a) an isolated nucleic acid molecule comprising sequence ID Nos., 1, 5, 9, 11, 13, or, 15, or complementary sequence thereof;

(b) an isolated nucleic acid molecule that specifically hybridizes to the nucleic acid molecule of (a) under conditions of high stringency; and

(c) an isolated nucleic acid that encodes a TGF-beta binding-protein according to (a) or (b).

2. The isolated nucleic acid molecule according to claim 1 wherein said nucleic acid molecule encodes a protein comprising the protein of Sequence ID NO. 2.

3. The isolated nucleic acid molecule according to claim 1 wherein said nucleic acid molecule encodes a protein comprising the protein of Sequence ID NO. 6.

4. The isolated nucleic acid molecule according to claim 1 wherein said nucleic acid molecule encodes a protein comprising the protein of Sequence ID NO. 10.

5. The isolated nucleic acid molecule according to claim 1 wherein said nucleic acid molecule encodes a protein comprising the protein of Sequence ID NO. 12.

6. The isolated nucleic acid molecule according to claim 1 wherein said nucleic acid molecule encodes a protein comprising the protein of Sequence ID NO. 14.

7. The isolated nucleic acid molecule according to claim 1 wherein said nucleic acid molecule encodes a protein comprising the protein of Sequence ID NO. 16.

8. An expression vector, comprising a promoter operably linked to a nucleic acid molecule according to any one of claims 1 to 7.

9. The expression vector according to claim 8 wherein said promoter is selected from the group consisting of CMV I-E promoter, SV40 early promoter and MuLV LTR.

10. The expression vector according to claim 8 wherein said promoter is a tissue-specific promoter.

11. A method of producing a TGF-beta binding protein, comprising, culturing a cell which contains a vector according to claim 8 under conditions and for a time sufficient to produce said protein.

12. The method according to claim 11, further comprising the step of purifying said protein.

13. A viral vector capable of directing the expression of a nucleic acid molecule according to any one of claims 1 to 7.

14. The viral vector according to claim 13 wherein said vector is selected from the group consisting of herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors and retroviral vectors.

15. A host cell carrying a vector according to any one of claims 8 to 14.

16. The host cell according to claim 15 wherein said cell is selected

from the group consisting of a human cell, dog cell, monkey cell, rat cell and mouse cell.

17. An isolated protein, comprising a TGF-beta binding-protein encoded by the nucleic acid molecule according to any one of claims 1 to 7.

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18. An antibody which specifically binds to the protein according to claim 17.

19. The antibody according to claim 18 wherein said antibody is a monoclonal antibody.

20. The antibody according to claim 19 wherein said monoclonal antibody is a murine or human antibody.

21. The antibody according to claim 18 wherein said antibody is selected from the group consisting of $F(ab')_2$, $F(ab)_2$, Fab', Fab, and Fv.

22. A hybridoma which produces an antibody according to claim 19.

23. A fusion protein, comprising a first polypeptide segment comprising a TGF-beta binding-protein encoded by the nucleic acid molecule according to any one of claims 1 to 7, or a portion thereof of at least 10 amino acids in length, and a second polypeptide segment comprising a non-TGF-beta binding-protein.

24. The fusion protein according to claim 23 wherein said first polypeptide segment is at least 20 amino acids in length.

25. The fusion protein according to claim 23 wherein said first polypeptide segment is at least 50 amino acids in length.

26. The fusion protein according to claim 23 wherein said second

polypeptide comprises multiple anionic amino acid residues.

27. An isolated oligonucleotide which hybridizes to a nucleic acid molecule according to Sequence ID NOs. 1, 3, 5, 7, 9, 11, 13, or 15, or the complement thereto, under conditions of high stringency.

28. The isolated oligonucleotide according to claim 27 wherein said oligonucleotide is at least 20 nucleotides in length.

29. The isolated oligonucleotide according to claim 27 wherein said oligonucleotide is at least 30 nucleotides in length.

30. The isolated oligonucleotide according to claim 27 wherein said oligonucleotide is at least 50 nucleotides in length.

31. The isolated oligonucleotide according to claim 27 wherein said oligonucleotide is between 50 to 100 nucleotides in length.

32. A pair of primers which specifically amplifies all or a portion of a nucleic acid molecule according to any one of claims 1 to 7.

33. A ribozyme which cleaves RNA encoding a protein according to claim 17.

34. The ribozyme according to claim 33 wherein said protein comprises the protein of Sequence ID NO. 2.

35. The ribozyme according to claim 33 wherein said protein comprises the protein of Sequence ID NO. 6.

36. The ribozyme according to claim 33 wherein said RNA encodes a protein comprising the protein of Sequence ID NO. 10.

37. The ribozyme according to claim 33 wherein said RNA encodes a protein comprising the protein of Sequence ID NO. 12.

38. The ribozyme according to claim 33 wherein said RNA encodes a protein comprising the protein of Sequence ID NO. 14.

39. The ribozyme according to claim 33 wherein said RNA encodes a protein comprising the protein of Sequence ID NO. 16.

40. The ribozyme according to claim 33 wherein said ribozyme is composed of ribonucleic acids.

41. The ribozyme according to claim 40 wherein one or more of said ribonucleic acids are 2'-O-methyl ribonucleic acids.

42. The ribozyme according to claim 33 wherein said ribozyme is composed of a mixture of deoxyribonucleic acids and ribonucleic acids.

43. The ribozyme according to claim 33 wherein said ribozyme is composed of nucleic acids having phosphothioate linkages.

44. A nucleic acid molecule comprising a nucleic acid sequence which encodes a ribozyme according to claim 33.

45. The nucleic acid molecule of claim 44, wherein the nucleic acid is DNA or cDNA.

46. The nucleic acid molecule of claim 44, under the control of a promoter to transcribe the nucleic acid.

47. A host cell comprising the ribozyme of claim 33.

48. A vector, comprising the nucleic acid molecule of claim 44.

49. The vector of claim 54, wherein the vector is a plasmid, a virus, retrotransposon or a cosmid.

50. The vector of claim 49 wherein said virus is selected from the group consisting of retroviruses, adenoviruses, and adeno-associated viruses.

51. A host cell containing the vector according to any one of claims 48 to 50.

52. The host cell according to claim 51 wherein said host cell is stably transformed with said vector.

53. The host cell according to claim 51 wherein the host cell is a human cell.

54. A method for producing a ribozyme, comprising providing DNA encoding the ribozyme according to claim 33 under the transcriptional control of a promoter, and transcribing the DNA to produce the ribozyme.

55. The method of claim 54 wherein the ribozyme is produced *in vitro*.

56. The method of claim 54, further comprising purifying the ribozyme.

57. A method for increasing bone mineralization, comprising introducing into a warm-blooded animal an effective amount of the ribozyme according to any one of claims 33 to 43.

58. A method of increasing bone mineralization, comprising

introducing into a patient an effective amount of the nucleic acid molecule of claim 44, under conditions favoring transcription of the nucleic acid molecule to produce a ribozyme.

59. A pharmaceutical composition, comprising the ribozyme according to any one of claims 33 to 43, and a pharmaceutically acceptable carrier or diluent.

60. A pair of primers capable of specifically amplifying all or a portion of a nucleic acid molecule according to any one claims 1 to 7.

61. A method for detecting a nucleic acid molecule which encodes a TGF-beta binding protein, comprising incubating an oligonucleotide according to any one of claims 27 to 31 under conditions of high stringency, and detecting hybridization of said oligonucleotide.

62. The method according to claim 61 wherein said oligonucleotide is labeled.

63. The method according to claim 61 wherein said oligonucleotide is bound to a solid support.

64. A method for detecting a TGF-beta binding protein, comprising incubating an antibody according to any one of claims 18 to 21 under conditions and for a time sufficient to permit said antibody to bind to a TGF-beta binding protein, and detecting said binding.

65. The method according to claim 64 wherein said antibody is bound to a solid support.

66. The method according to claim 64 wherein said antibody is labeled.

67. The method according to claim 66 wherein said antibody is labeled with a marker selected from the group consisting of enzymes, fluorescent proteins, and radioisotopes.

68. A transgenic animal whose germ cells and somatic cells contain a nucleic acid molecule encoding a TGF-beta binding-protein according to claim 1 which is operably linked to a promoter effective for the expression of said gene, said gene being introduced into said animal, or an ancestor of said animal, at an embryonic stage, with the proviso that said animal is not a human.

69. The transgenic animal according to claim 68 wherein TGF-beta binding-protein is expressed from a vector according to any one of claims 8 to 10.

70. A transgenic knockout animal, comprising an animal whose germ cells and somatic cells comprise a disruption of at least one allele of an endogenous nucleic acid molecule which hybridizes to the nucleic acid molecule according to claim 1, wherein said disruption prevents transcription of messenger RNA from said allele as compared to an animal without said disruption, with the proviso that said animal is not a human.

71. The transgenic animal according to claim 70 wherein said disruption is a nucleic acid deletion, substitution, or, insertion.

72. The transgenic animal according to claim 68 or 70 wherein the animal is selected from the group consisting of a mouse, a rat and a dog.

73. A method for determining whether a candidate molecule is capable of increasing bone mineral content, comprising:

(a) mixing one or more candidate molecules with TGF-beta-binding-protein encoded by the nucleic acid molecule according to any one of claims 1 to 7 and a selected member of the TGF-beta family of proteins;

(b) determining whether the candidate molecule alters the signaling of the TGF-beta family member, or alters the binding of the TGF-beta binding-protein to the TGF-beta family member.

74. The method according to claim 73 wherein said member of the TGF-beta family of proteins is BMP6.

75. A method for determining whether a candidate molecule is capable of increasing bone mineral content, comprising: determining whether a candidate molecule inhibits the binding of TGF-beta binding-protein to bone, or an analogue thereof.

76. The method according to claim 75 wherein said analogue of bone is hydroxyapatite.

77. A kit for detection of TGF-beta binding-protein gene expression, comprising a container that comprises a nucleic acid molecule, wherein said nucleic acid molecule is selected from the group consisting of (a) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1, 5, 7, 9, 11, 13, or 15; (b) a nucleic acid molecule comprising the complement of the nucleotide sequence of (a); (c) a nucleic acid molecule that is a fragment of (a) or (b) of at least 20 nucleotides in length.

78. A kit for detection of TGF-beta binding-protein, comprising a container that comprises an antibody according to any one of claims 18 to 21.

79. An antisense oligonucleotide, comprising a nucleic acid molecule which hybridizes to a nucleic acid molecule according to Sequence ID NOs. 1, 3, 5, 7, 9, 11, 13, or 15, or the complement thereto, and wherein said oligonucleotide inhibits the expression of TGF-beta binding protein according to claim 17.

80. The oligonucleotide according to claim 79 wherein said

oligonucleotide is 15 nucleotides in length.

81. The oligonucleotide according to claim 79 wherein said oligonucleotide is 20 nucleotides in length.

82. The oligonucleotide according to claim 79 wherein said oligonucleotide is 50 nucleotides in length.

83. The oligonucleotide according to claim 79, wherein said oligonucleotide is comprised of one or more nucleic acid analogs.

84. The oligonucleotide according to claim 79, wherein said oligonucleotide is comprised of one or more ribonucleic acids.

85. The oligonucleotide according to claim 79, wherein said oligonucleotide is comprised of one or more deoxyribonucleic acids.

86. The oligonucleotide according to claim 79 wherein said oligonucleotide sequence comrpises one or more modified covalent linkages.

87. The oligonucleotide according to claim 86 wherein said modified covalent linkage is selected from the group consisting of a phosphorothioate linkage, a phosphotriester linkage, a methyl phosphonate linkage, a methylene(methylimino) linkage, a morpholino linkage, an amide linkage, a polyamide linkage, a short chain alkyl intersugar linkage, a cycloalkyl intersugar linkage, a short chain heteroatomic intersugar linkage and a heterocyclic intersugar linkage.

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